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| 10/501,028 | 03/14/2005 | Christopher M. Starr | 7685-93 | 1759 |

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BERESKIN AND PARR
40 KING STREET WEST
BOX 401
TORONTO, ON M5H 3Y2
CANADA

| EXAMINER | |
|---|---|
| SRIVASTAVA, KAILASH C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1657 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/501,028 | STARR ET AL. | |
| | Examiner | Art Unit | |
| | Dr. Kailash C. Srivastava | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *6,15 and 21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

# DETAILED ACTION

1. The response filed 08 November 2007 to Election requirement in Office Actions mailed 09 May 2007 is acknowledged and entered.

## Claims Status

2. Claims 1-29 are pending.

## *Restriction/Election*

3. Election of Group I invention encompassing Claims 1-20, consisting of:

   a. Claims 1-13 drawn to a method to treat a subject having a lysosomal storage disease via administering to said subject a composition comprising a p97 molecule covalently linked to a protein;

   b. consisting of Claims 14-20 drawn to a p97 molecule covalently linked to a protein; and

additional election of following species:

(i) Sandhoff disease from Claim 12; and

(ii) protein- β-hexosaminidase A from Claims 13 and 20,

in response filed 08 November 2007 is acknowledged and entered.

Because applicant did not distinctly and specifically traverse the election requirement cited supra, the election has been treated as an election without traverse (See M.P.E.P. §818.03(a)). Accordingly, the restriction requirement is deemed proper and is made FINAL.

4. Accordingly, Claims 6, 15 and 21-29 and additional species recited in Claims 12-13 and 20 are withdrawn from further consideration as being directed to a non-elected invention. See 37 C.F.R. §1.142(b) and M.P.E.P. § 821.03.

5. Claims 1-20 drawn to a method to treat a subject having a lysosomal storage disease and a composition comprising a p97 molecule covalently linked to a protein and species Sandhoff disease and β-hexosaminidase are examined on merits.

## Priority

6. Priority claim under 35 U.S. C. §119 (f) to U. S. Non-provisional Application, Serial number 60/347,758 filed 11 January 2002 and to PCT/US03/00894 filed 10 January 2003 respectively is acknowledged.

## Objection To Specification

7. The specification is objected to because Line one of first page of specification, in its present form does not cite the application priority data. Please update Priority Data at Line 1 of the First Page of the Specification to encompass PCT/US02/00894.

## Objection To Claims

8. Claim 10 at Line 1 is objected to because of "as" before the word, "sequence". Appropriate correction/clarification is needed.

## Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Long*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

10. Claims 14-20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 and 2 of copending U.S. Provisional Application Number 10/588,425. Although, conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-2 of the referenced applicaation are drawn to a composition comprising the same proteins (e.g., β-hexosaminidase A and L-iduronidase) as instantly claimed. The instantly claimed Claims 14-20 are drawn

to a composition comprising same enzymes as proteins. Said composition is applicable to treat a subject having a lysosomal storage disease (Please see instantly claimed Claims 1-13).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

## Claim Rejections - 35 U.S.C. §112

11. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

12. Claim 10 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Phrase, "sequence which is 90% identical to the sequence of a corresponding domain of human p97", renders Claim 10 unclear, vague and therefore indefinite. This is because in absence of the sequence for the base p97 molecule, there is no basis for comparing the "90% identity". Thus, Claim 10 fails to particularly point out and distinctly claim the "complete" method. The metes and bounds of the claimed method are therefore not clearly established or delineated.

## *Claim Rejections - 35 U.S.C. §103*

13. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § *103*(c) and potential 35 U.S.C. § ***102***(f) or (g) prior art under 35 U.S.C. § 103(a).

15. Claims 1-5, 7-14 and 16-20 are rejected under 35 U.S.C. §103(a) as obvious over the combined teachings from Newel (US Patent 4,866,042) in view of Jeffries et al (US Patent 5,981,194) and

WikiPedia Foundation, Inc., (See Sandhoff disease, http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008) and further in view of LeBowitz (USPGPB 2003/0072761 A1).

Claims are drawn to a method and a composition, wherein a composition, a conjugate, comprising soluble human·p97 covalently linked to a protein by a linker of 5-20 carbon atoms is intravenously administered to a subject in need thereof to treat a lysosomal storage disease. said conjugate passes through the blood brain barrier (i.e., BBB). In said composition, the lysosomal storage disease is Sandhoff disease and the protein is β-hexosaminidase A.

Neuwelt teaches, lysosomal storage diseases are the result of blood brain barrier (i.e., BBB) because of the genetic disorders causing absence of hydrolases in the lysosomes so that the substrates for those enzymes (e.g., alpha-L-iduronidase) may accumulate (Column 1, Lines 15-68). Neuwelt further teaches a method to treat said diseases through delivering/incorporating directly into the human/subject brain tissue in need thereof, the corrective genetic material or compound comprising the lacking moiety (e.g., a ligand, an enzyme or enzyme substrate). Said material is injected intravenously or intra-arterially, followed by injecting a hyper-osmotic solution of a compound (e.g., mannitol) that temporarily disrupts the BBB (Column 9, Line 30 to Column 10, Line 28; Column 13, Line 25 to Column 14, Line 13). Said material is a pharmaceutical composition because according to Neuwelt it is prepared via inserting the appropriate compound/ human genetic material into a non-infective retrovirus genome, annealing said genome, and closing the vector with a linker that is complimentary to both the vector and the inserted material (Column 8, Lines 29-68; Column 14, Lines 1-30). Prior to injecting said composition in the subject in need thereof, said preparation is screened for therapeutic activity to pass through the BBB via labeling the vector with radioactive sulphur (i.e., $^{35}S$). Subsequently a pharmaceutical composition comprising non-labeled (i.e., without 35S) said preparation is injected to the subject in need thereof. Because the genome of viral vector together with viral envelope is conjugated to a protein, Neuwelt teaches treating a lysosomal storage disease via administering a pharmaceutical composition comprising a protein covalently conjugated to a material whose deficiency causes said disease. The atom chain length for said linker is intrinsically the same as claimed because the prior art teaches a composition comprising same ingredients and steps as claimed instantly. Please note, Sandhoff disease is a GM2 gangliosidoses **Sandhoff disease**) related diseases caused by the deficiency of β-hexosaminidase A (See Sandhoff disease, Wikimedia Foundation, Inc., http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008). Neuwelt, however, does not clarify that the material administered is a soluble

(p97 molecule, the linker is polyethylene glycol, or a linking group is 4-20 atom length.

Jeffries et al. clearly teach soluble p97 (e.g., Column 6, Lines 21-23) and its application in modulating iron uptake in cells, or controlling binding of p97 to receptors in brain endothelial cells in such manner to treat Alzheimer's, among other diseases (Column 6, Lines 45-57). They further teach a composition for delivering an agent across the BBB comprising p97 in association with a pharmaceutical carrier, wherein p97 is conjugated to the substance to be delivered in a pharmaceutical composition (Column 8, Lines 54-67) via incorporating p97 into vesicles, viral envelopes or cells or DNA to correct defective genetic material (Column 31, Lines 49-67). Jeffries et al. also teach compositions comprising p97 and delivering it to the subject in need thereof to diagnose, monitor and treat a lysosomal storage disease, i.e. Alzheimer's (Column 101, Line 25 to Column 102, Line 2).

LeBowitz teaches Sendoff Disease is caused by deficiency in β-hexosaminidase A and teaches compositions comprising and delivering therapeutic agents and fusion proteins comprising said material to overcome enzymatic defects associated with lysosomal storage disease (Table 1, Line18; Page 5, Column 2, Paragraphs 0057-0058; Paragraphs 0062-0063; Example 5).

One having ordinary skill in the art at the time of claimed invention would have been motivated to combine the teachings from Neuwelt with the beneficial teachings from Jeffries et al., and LeBowitz; because Jeffries et al. in contrast to Neuwelt's teachings expressly define a composition comprising p97 to be delivered to a subject in need of said pharmaceutical composition in diagnosing, monitoring and treating lysosomal storage disease the p97 and LeBowitz teaches that Sandhoff Disease is because of the absence or defect in the presence of β-hexosaminidase A and is corrected by administering to an individual in need of a composition comprising β-hexosaminidase A that is a fusion protein. The actual concentrations of individual components for preparation of said pharmaceutical composition may not be the same as instantly claimed. However, the adjustment of particular conventional working components/ conditions (e.g., types of complimentary materials having same physiological effects and concentrations thereof) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan. In view of the fact that the applicant's invention also recites composition comprising same components, and methods comprising the same steps and ingredients as are disclosed in prior art teachings; applicant's invention is obvious over the teachings of Examiner-cited prior art references.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify/combine the teachings from Neuwelt with the beneficial teachings from Jeffries et al., and LeBowitz; because Jeffries et al. remedy the deficiency in Neuwelt's teachings of expressly defining a composition comprising p97 to be delivered to a subject in need of said pharmaceutical composition in diagnosing, monitoring and treating lysosomal storage disease the p97 and LeBowitz teaches that Sandhoff Disease is because of the absence or defect in the presence of β-hexosaminidase A and is corrected by administering to an individual in need of a composition comprising β-hexosaminidase A that is a fusion protein. The actual concentrations of individual.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

## Conclusion

16. No Claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1657
(571) 272-0923

18 January 2008

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1657